

# Mastocytosis and adverse reactions to biogenic amines and histamine-releasing foods: what is the evidence?

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## ABSTRACT

**Background:** It has been suggested that normal concentrations of biogenic amines and 'histamine-releasing foods' may exacerbate symptoms in mastocytosis. The purpose of this study was to look for scientific evidence in the literature on diets restricted in biogenic amines and histamine-releasing foods in the treatment of mastocytosis.

**Methods:** Medline (1966 to 2004), Cinahl (1982 to 2004) and the Cochrane Library were searched for double-blind placebo-controlled food challenge (DBPCFC) studies with biogenic amines and/or histamine-releasing foods in mastocytosis.

**Results:** No studies employing DBPCFC with dietary biogenic amines or histamine-releasing foods in mastocytosis were found. Only a few *in vitro* studies in other diseases, animal studies and studies in humans in which histamine-releasing agents were incubated directly with duodenal tissues were found. One case was reported of severe adverse reactions to alcohol in mastocytosis, objectified by an open challenge.

**Conclusion:** Despite the widespread belief that biogenic amines and histamine-releasing foods may cause allergy-like, non-IgE-mediated symptoms in certain patients, the role of diets restricted in biogenic amines and histamine-releasing foods in the treatment of mastocytosis remains hypothetical but worthy of further investigation. There is some evidence for adverse reactions to alcohol in mastocytosis.

## KEYWORDS

Adverse reactions, biogenic amines, double-blind placebo-controlled food challenge, histamine-releasing foods, mastocytosis

## INTRODUCTION

Mastocytosis is an uncommon disorder characterised by the accumulation of mast cells in various tissues including bone marrow in the systemic form of the disease. The essential role of mast cells in allergic diseases was recognised a long time ago but the physiological role of mast cells is still unclear. However, there is substantial evidence that mast cells may play a key role in acquired and innate immune responses in host defences against micro-organisms<sup>1,2</sup> and in wound healing and angiogenesis.<sup>3</sup> Besides the well-known triggering of degranulation of mast cells by crosslinking of the FcεRI receptor by specific allergens, several other stimuli such as neuropeptides (substance P), complement factors (C3a, C5a), lipoproteins, adenosine and superoxides may activate mast cells.<sup>3</sup>

It has been suggested that foods containing high but nontoxic levels of biogenic amines and the 'histamine-releasing foods' may exacerbate symptoms in mastocytosis. Alcohol is also considered to be a triggering factor in mast cell degranulation.<sup>4</sup> Therefore, it has been suggested that diets restricted in biogenic amines or histamine-releasing foods may be beneficial for some patients with systemic mastocytosis. However, many authorities do not mention diet intervention as a common therapeutic measure,<sup>5</sup> whereas others suggest certain foods to be a possible trigger, but only in certain patients.<sup>4</sup>

The purpose of this study was to verify in the literature if there is any evidence for the putative beneficial effects of elimination diets restricted in biogenic amines or histamine-releasing foods.

### Biogenic amines

Biogenic amines are normal constituents of many foods. These low-molecular-weight organic bases are formed in plants and animals, and also endogenously in the human body. Biogenic amines arise in foods by enzymatic decarboxylation of free amino acids.<sup>6</sup> Biogenic amines are divided into monoamines, such as tyramine, serotonin, phenylethylamine, dopamine, epinephrine and norepinephrine, and diamines, such as histamine, cadaverine and putrescine. Adverse reactions to foods are most frequently reported in foods containing high levels of tyramine and histamine, which is referred to as histamine poisoning or scrombroid poisoning.<sup>7</sup> This intoxication is caused by high levels of histamine, for example in spoiled scrombroid fish, such as tuna and mackerel. Tyramine and histamine are formed by decarboxylation of tyrosine and histidine respectively, both amino acids.<sup>6,7</sup>

Endogenously synthesised biogenic amines fulfil important metabolic functions in the body. Histamine plays a role in normal and abnormal biological processes, including vasodilatation, gastric acid secretion and allergic reactions.

In contrast to histamine, tyramine is vasoconstrictive and may cause an increase in blood pressure.

Generally, monoamine oxidases (MAO A and MAO B) and diamine oxidase (DAO) play a major role in the catabolism of monoamines and diamines, respectively. These enzymes are located in the gastrointestinal tract, and also in the liver, lung, platelets, spleen and kidneys. These enzymes prevent the absorption of unmetabolised biogenic amines into the circulation. The metabolism of histamine is depicted in *figure 1*. There are two main enzymatic pathways:

- Histamine is converted by histamine methyltransferase (HMT) to methylhistamine (MH), and subsequently metabolised by MAO to methylimidazole acetic acid (MIMA) or
- histamine is deaminated by DAO to imidazole acetic acid (IAA).<sup>8</sup>

Dietary biogenic amines are especially found in aged and fermented food, and in foods containing relatively high amounts of free amino acids.<sup>9</sup> Most notably, ripened cheese, fermented meat, smoked and tinned fish, sauerkraut and fermented yeast and fermented soy products usually contain significant amounts of histamine. Concentrations of histamine may vary considerably and a daily dietary intake of histamine of 100 to 200 mg can easily be reached, depending on the foods chosen. In *tables 1* and *2*, the

**Table 1** *Foods rich in histamine*

Food categories	Mg histamine/100 gram	Mg histamine/serving
<b>Cheese:</b> Gouda, Cheddar, Danish Bleu, Emmenthaler, goats cheese, Gorgonzola, Mascarpone, Parmesan	3.3-171	0.7-35 (20 gram)
<b>Meat:</b> fermented meat, hare, (dry) sausage, raw ham	3.0- 27	0.6-5.5 (20 gram)
<b>Fish:</b> herring, smoked mackerel, tinned fish (sardines), tuna fish, anchovy products	0.8-16.5 95-344	0.6-11.5 (70 gram) 9.5-34 (10 gram)
<b>Vegetables:</b> egg plant, spinach, sauerkraut	2.5-11.5	5-23 (200 gram)
<b>Alcoholics:</b> beer and wine	0.6-1.6	0.6-1.6 (100 ml) 1.2-2.2 (200 ml)
<b>Fermented foods:</b> Tamari, marmite, trassi, tempe	8.3-212	0.8-21 (10 gram)

**Table 2** *Foods rich in tyramine*

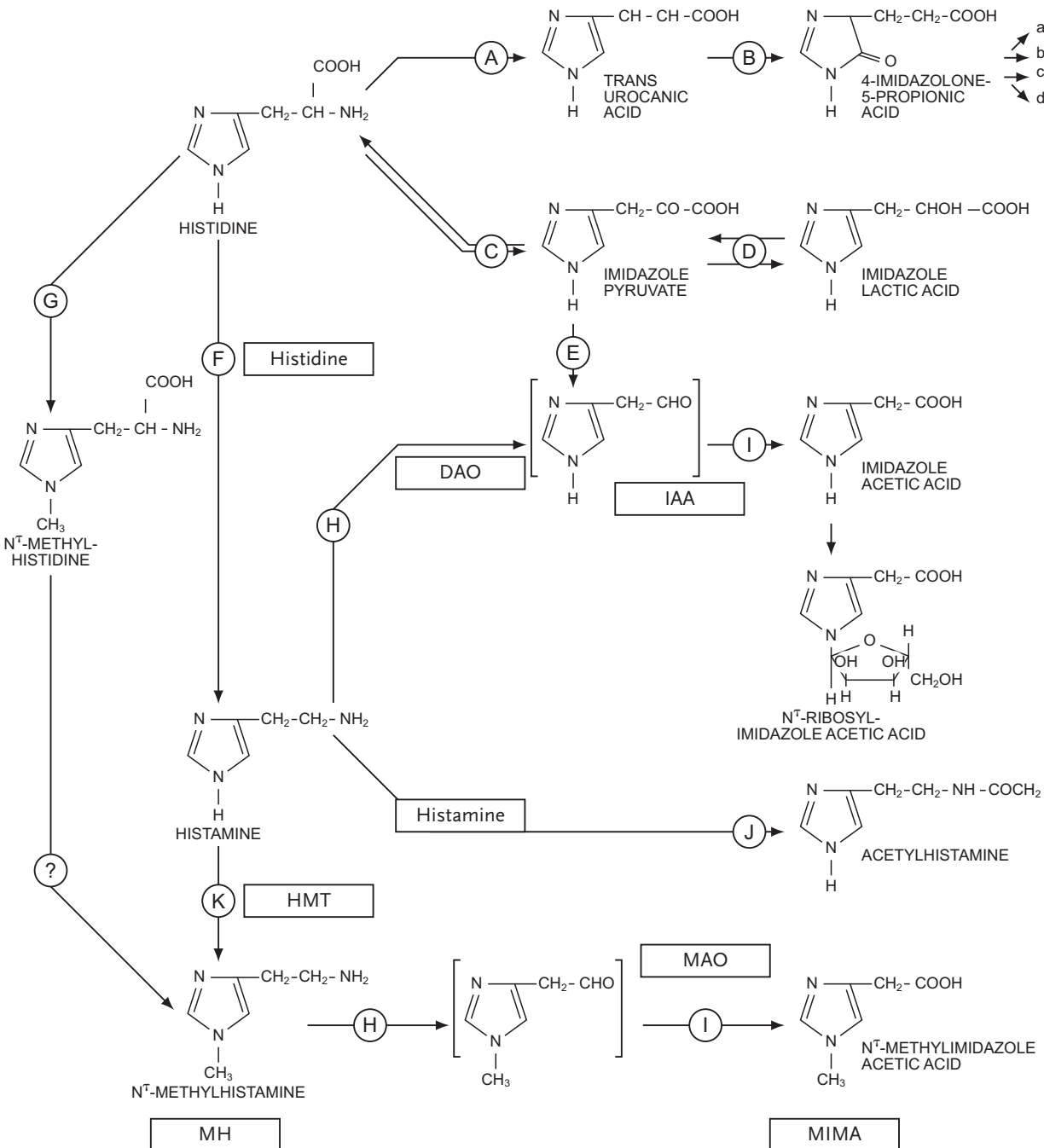
Food categories	Mg tyramine/100 gram	Mg tyramine/serving
<b>Cheese:</b> most cheeses	5.0-152	1.0-31 (20 gram)
<b>Chocolate</b>	0.8	0.2 (25 gram)
<b>Meat:</b> fermented meat, hare, (dry) sausage, raw ham	8.5-56	1.7-11 (20 gram)
<b>Fish:</b> smoked fish, tinned fish (sardines, tuna), shrimps, anchovy products	2.5-12.9 6.4-13	1.8-9 (70 gram) 0.6-1.3 (10 gram)
<b>Vegetables:</b> egg plant, spinach, sauerkraut	6.1-16.5	12.2-33 (200 gram)
<b>Alcoholics:</b> beer and wine	0.5-3.6	0.5-3.6 (100 ml) 1.0-7.2 (200 ml)
<b>Fermented foods:</b> soy sauce, marmite, trassi, tempe	15-178	1.5-18 (10 gram)

respective amounts of histamine and tyramine in mg per serving in food categories rich in biogenic amines are shown. In *table 3* some foods low in histamine in these food categories are shown.

## Histamine-releasing foods

Many foods or food components are considered to have the capacity to release histamine directly from tissue mast cells in the body.<sup>9</sup> These foods are listed in *table 4*.

**Figure 1** *Metabolism of histidine and histamine<sup>8</sup>*



DAO = diamine oxidase (or histaminase); IAA = imidazole acetic acid; HMT = histamine methyltransferase; MAO = monoamine oxidase; MH = methylhistamine; MIMA = methylimidazole acetic acid.

**Table 3** *Exceptions: Foods low in histamine*

Food categories	Mg histamine/100 gram
<b>Cheese:</b> Edam, Brie, Camembert, Feta, Mozzarella	0.0-0.3
<b>Fish:</b> fresh/frozen fish (codfish, salmon, sole, whiting, place, crab, mussels)	0.0-0.1
<b>Chocolate</b>	0.1
<b>Fermented foods:</b> tofu	0.1

**Table 4** *Foods with suggested histamine-releasing capacities*

Additives	Alcohol	Chocolate
Citrus fruit	Crustaceans	Egg white
Fish	Liquorice	Nuts
Papaya	Peanuts	Pineapple
Pork	Spices	Spinach
Strawberries	Tomatoes	

## MATERIALS AND METHODS

Medline (1966-2004), Cinahl (1982-2004) and the Cochrane Library were searched in the English and German language for clinical studies on adverse reactions to biogenic amines and histamine-releasing foods in mastocytosis. Clinical studies were defined as studies employing dietary elimination followed by DBPCFC studies with biogenic amines or histamine-releasing foods in human beings with suspected or confirmed mastocytosis. For studies on biogenic amines the keywords (biogenic amin\* or histamin\* or methylhistamin\*) were combined with (mastocytosis or systemic mastocytosis or mast cell disease or urticaria pigmentosa) and (food or diet or hypersens\* or adverse or intolerant or intolerance or allerg\* or toxicity or nonIgE). For studies on histamine-releasing effects of foods the keywords (histamine releas\* or releas\*) were combined with (mastocytosis or systemic mastocytosis or mast cell disease or urticaria pigmentosa) and (food or diet or hypersens\* or adverse or intolerant or intolerance or allerg\* or toxicity or nonIgE).

## RESULTS

No clinical studies employing DBPCFC were found on (adverse) effects of dietary biogenic amines in mastocytosis, or on (adverse) effects to histamine-releasing foods. Only one study employing an open food challenge with histamine rich foods was found.<sup>10</sup> In this study Vidal and others described a patient with a rare form of cutaneous masto-

cytosis (telangiectasia macularis eruptiva perstans) suspected to suffer from adverse reaction to fish, but in whom open food challenges with fresh crayfish, shrimp and tuna were negative.

Studies in human beings on the putative histamine-releasing effects of foods are limited to reports of such effects on *ex vivo* duodenal tissue performed by Moneret-Vautrin and coworkers.<sup>11</sup> They showed that incubating duodenal biopsy material with various histamine-releasing pharmacological agents, such as compound 48/80, Concanavalin A, the calcium ionophore A 23187, and anti-IgE resulted in increased nonspecific release of histamine by duodenal mast cells. They demonstrated that in subjects with non-IgE-mediated adverse reactions to food, duodenal mucosal biopsies show massively degranulated cells in sharp contrast to those seen in controls.

According to these authors, these findings support the hypothesis that the digestive mucosal mast cells may be abnormally sensitive to histamine liberation in some subjects.<sup>12</sup> However, they showed no *in vivo* data to support the relevance of these findings. In addition, we found no clinical studies using oral challenge tests to support the hypothesis for the histamine-releasing capacity of foods. Only a few *in vitro* studies and animal studies in other diseases have demonstrated histamine-releasing effects of foods or food components, but no literature on this subject was found dating from the last two decades. Schachter and Talesnik found in 1952 that egg white releases histamine in nonsensitized animals when injected intravenously.<sup>13</sup> In this article the authors refer to unpublished data by Schachter on histamine-releasing effects of strawberries and to a publication on histamine liberation by shellfish, published by WDM Paton in 1954 in *J Physiol* 1954;123:58P, and by E. Urbach in *Allergy* 1946, Heineman, London. We were not able to obtain a copy of these old articles to verify their conclusions. In some studies, it was demonstrated *in vitro* that in both chronic urticaria patients and controls, food additives were able to release histamine from leucocytes.<sup>14,15</sup> However, no differences between patients and controls were found. Baenkler and coworkers conducted *in vitro* tests with wheat, egg, milk and fish on the mucosa of patients suffering from several intestinal diseases, including patients suffering from food intolerance and inflammatory diseases.<sup>16</sup> In all these patients skin tests with these foods were negative. Significant differences were found in histamine-release between patient groups. Surprisingly, the smallest amount of histamine release was found in the food-intolerant patients, the largest amount in the inflammatory group. We could not find any study on histamine-releasing effects of most of the foods suggested of having histamine-releasing capacities, as shown in *table 4*.

In one case, adverse effects to alcohol in mastocytosis were reported. Bandmann *et al.* described a patient with anaphylactic-like reactions to alcohol, objectified by open challenge.<sup>17</sup> This patient reacted to 20 ml of cognac with flush, tachycardia, severe headache and diarrhoea.

## DISCUSSION

Despite the widespread belief that biogenic amines and histamine-releasing foods may cause allergy-like, non-IgE-mediated symptoms in certain patients, our literature search failed to identify any clinical study in patients with mastocytosis employing DBPCFC to demonstrate putative adverse effects of these foods and food components. Several hypotheses have been formulated to explain such putative adverse reactions to normal amounts of biogenic amines, although these hypotheses have not been put forward in relation to mastocytosis. Firstly, a decreased level of DAO is said to be a cause of intolerance to biogenic amines. Some studies showed a decreased level of DAO in patients with atopic dermatitis and chronic urticaria.<sup>18-21</sup> Secondly, inhibiting effects of substances on DAO, MAO or HMT might be other causes for intolerance to biogenic amines. Many inhibitors of MAO, DAO or HMT in food have been identified.<sup>7</sup> For example, other biogenic amines such as tyramine might inhibit these enzymes and could theoretically potentiate histamine intoxication. Furthermore, there have been numerous reports on hypertensive crises in patients using MAO-inhibiting drugs<sup>22</sup> in combination with foods rich in tyramine. Remarkably, there are no data available on the hazardous effect of MAO-inhibiting drugs and histamine release in patients with mastocytosis. Thirdly, the barrier disruptive hypothesis has been described by Taylor.<sup>7</sup> This hypothesis holds that several potentiators might interfere with the protective function of intestinal mucin. These potentiators, such as cadaverine and putrescine (other biogenic amines), would bind to mucine and in this way facilitate an increased absorption of histamine. There is a lack of evidence supporting these putative mechanisms and no clinical studies suggesting that these mechanisms might be operative. A recent literature survey from 1966 to 2001 by Jansen *et al.* on adverse reactions to biogenic amines showed no supportive evidence for the relation to migraine, headache or wine intolerance. In relation to chronic urticaria no methodologically sound studies were found.<sup>23</sup> In one DBPCFC study in healthy volunteers,<sup>24</sup> symptoms such as headache, dizziness and discomfort in 11 out of 54 challenges were found after 5 mg phenylethylamine, but not after 25 mg histamine or 25 mg tyramine. There is no convincing evidence that patients with mastocytosis have increased releasability of mast cells as compared with normal mast cells. It is generally thought that

symptoms resulting from mediator release are due to high mast cell load,<sup>4,5</sup> rather than to increased releasability. Furthermore, there are no DBPCFC studies in human beings supporting the widely held belief that foods should have histamine-releasing capacity. The hypothesis that foods may have a histamine-releasing capacity is based on several older *in vitro* studies, animal studies in other diseases demonstrating histamine-releasing effects of foods, and on studies in which pharmacological substances were incubated directly with digestive tract mucosal tissues. Thus, the normal digestive influences on foods are eliminated and the significance of these findings is doubtful. The Committee of Adverse Reactions to Foods of the American Academy of Allergy and Immunology<sup>25</sup> concluded in 1984 that the effects of such foods are 'unproven'. Taken together, the theories on adverse reactions to normal amounts of biogenic amines and the histamine-releasing capacities of foods in patients with mastocytosis are unproven. However, the persistence of these theories on adverse reactions to biogenic amines and the histamine-releasing capacity of foods suggest that further investigation is necessary to confirm or reject the putative effects of these food substances.

Adverse reactions to alcohol may be relevant in some patients with mastocytosis, although the prevalence of this phenomenon is unknown.<sup>17</sup> The explanation for the documented anaphylactic reaction to alcohol in mastocytosis can be found in similar metabolic pathways for alcohol and histamine;<sup>5,26</sup> alcohol and acetaldehyde inhibit DAO, which results in elevated histamine levels. Furthermore, acetaldehyde has shown to have a degranulating and histamine-releasing effect on mast cells.<sup>26-28</sup> Elevated concentrations of histamine metabolites are found in patients with mastocytosis. Although measurement of serum tryptase is currently being used in diagnosing mastocytosis,<sup>4,5</sup> in some centres the measurement of urinary excretion of the histamine metabolites MIMA and MH is used as an additional biochemical marker for mastocytosis. These metabolites are formed endogenously, but also dietary intake enhances the urinary excretion of these amines.<sup>6-8,29</sup> Furthermore, Keyzer and others found that a diet high in protein (138 g) with exclusion of foods that may be rich in histamine significantly enhances the amount of MH.<sup>29</sup> This is caused by high levels of tyramine in diets rich in protein. Therefore, dietary restrictions in histamine and protein intake before urinary sampling of histamine metabolites are justified.

In conclusion, a review of the literature provided no sound scientific support for beneficial effects of diets restricted in biogenic amines and histamine-releasing foods in patients with mastocytosis. Therefore, the role of these diets in the treatment of mastocytosis remains hypothetical. However, systematic studies have not been carried out and further investigation is warranted. Such studies should

confirm putative adverse effects of these foods and food components by DBPCFC. Although there is little evidence incriminating alcohol as a cause of adverse reactions in patients with systemic mastocytosis, caution is probably warranted until more studies have been done.

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## NOTE

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